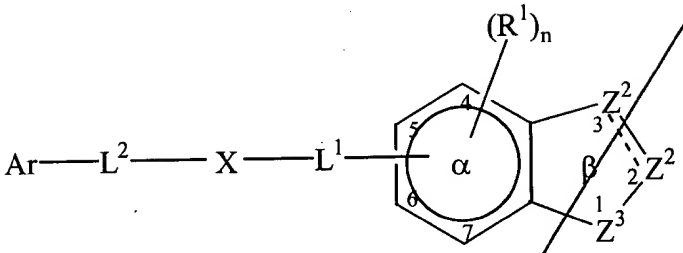
Claims

1. A compound of the formula:



(1)

and the pharmaceutically acceptable salts thereof, or a pharmaceutical composition thereof, wherein:

Ar is an aryl group substituted with 0-5 non-interfering substituents, wherein two adjacent noninterfering substituents can form a fused aromatic or nonaromatic ring;

L^1 and L^2 are linkers;

X is an aliphatic monocyclic or aliphatic polycyclic moiety optionally comprising one or more hetero ring atoms wherein the cyclic moiety may be optionally substituted with one or more noninterfering substituents and where said optional substituents may constitute a ring fused to X;

n is 0-3;

each R^1 is hydrogen or a noninterfering substituent;

⫽ represents a single or double bond;

one Z^2 is CA or CR^2A; the other Z^2 is CR^3, CR^3_2, NR^4 or N; and each R^2, R^3 and R^4 is independently hydrogen or a noninterfering substituent;

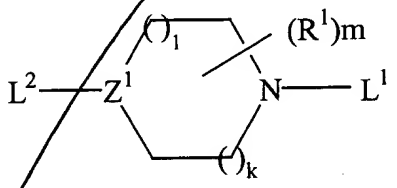
Z^3 is NR^5 or O; where R^5 is hydrogen or a noninterfering substituent;

A is $-W_i-COX_jY$, where Y is COR^6 or an isostere thereof, each of W and X is a spacer of 2-6Å; each of i and j is independently 0 or 1; and R^6 is a noninterfering substituent;

and wherein the smallest number of covalent bonds in the compound separating the atom of Ar linked to L^2 and the atom of the α ring linked to L^1 is at least 5, each said

bond having a bond length of 1.2 to 2.0 angstroms; and/or the distance in space between the atom of Ar linked to L^2 and the atom of the α ring linked to L^1 is 4.5 –24 angstroms;

and with the proviso that the portion of the compound represented by L^2-X-L^1 is not:



where L^2 and L^1 are linkers; Z^1 is CR or N wherein R is hydrogen or a non-interfering substituent; each R^1 is independently a non-interfering substituent; and each of l and k is 0-3; and m is 0-4.

2. The compound of claim 1 wherein A is $COXjCOR^6$, and

wherein R^6 is H, or is straight or branched chain alkyl, alkenyl, alkynyl, aryl, arylalkyl, heteroalkyl, heteroaryl, or heteroarylalkyl, each optionally substituted with halo, alkyl, heteroalkyl, SR, SOR, SO_2R, SO_2NR_2, OR, NR_2, OCOR, NRCOR, $NRCONR_2$, $NRSO_2R$, $NRSO_2NR_2$, $OCONR_2$, CN, COOR, $CONR_2$, COR, or R_3Si wherein each R is independently H, alkyl, alkenyl or aryl or the heteroatom-containing forms thereof, or

wherein R^6 is OR, NR_2, SR, $NRCONR_2$, $OCONR_2$, or $NRSO_2NR_2$, wherein each R is independently H, alkyl, alkenyl or aryl or the heteroatom-containing forms thereof, and wherein two R attached to the same atom may form a 3-8 member carbocyclic or heterocyclic ring and wherein said ring may further be substituted by alkyl, alkenyl, alkynyl, aryl, arylalkyl, heteroalkyl, heteroaryl, heteroarylalkyl, each optionally substituted with halo, SR, OR, NR_2, OCOR, NRCOR, $NRCONR_2$, $NRSO_2R$, $NRSO_2NR_2$, $OCONR_2$, or R_3Si wherein each R is independently H, alkyl, alkenyl or aryl or the heteroatom-containing forms thereof wherein two R attached to the same atom may form a 3-8 member ring, optionally substituted as above defined; and

X, if present, is CR_2, wherein R is independently H, alkyl, alkenyl or aryl or the heteroatom-containing forms thereof wherein two R attached to the same atom may form a 3-8 member ring, optionally substituted as above defined.

3. The compound of claim 1 wherein Y is an isostere of COR^6.

4. The compound of claim 3 wherein Y is tetrazole; 1,2,3-triazole; 1,2,4-triazole; or imidazole.

5. The compound of claim 1 wherein each of i and j is 0.

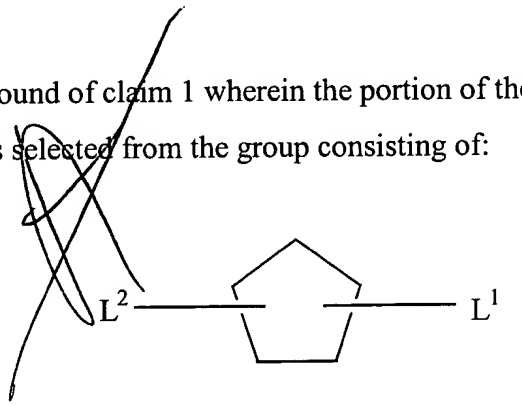
6. The compound of claim 2 wherein j is 0.

7. The compound of claim 1 wherein Z^3 is NR^5.

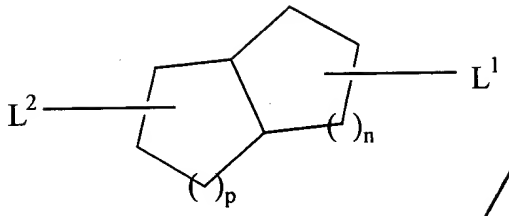
8. The compound of claim 7 wherein R^5 is H or is optionally substituted alkyl, alkenyl, alkynyl, aryl, arylalkyl, acyl, aroyl, heteroaryl, heteroalkyl, heteroalkenyl, heteroalkynyl, heteroalkylaryl, or is SOR, SO_2R, RCO, COOR, alkyl-COR, SO_3R, $CONR_2$, SO_2NR_2, CN, CF_3, NR_2, OR, alkyl-SR, alkyl-SOR, alkyl-SO_2R, alkyl-OCOR, alkyl-COOR, alkyl-CN, alkyl-$CONR_2$, or R_3Si, wherein each R is independently H, alkyl, alkenyl or aryl or heteroforms thereof.

9. The compound of claim 8 wherein R^5 is H, or is optionally substituted alkyl or acyl.

10. The compound of claim 1 wherein the portion of the compound represented by L^2-X-L^1 is selected from the group consisting of:

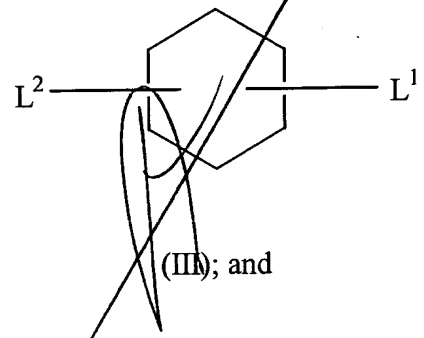


(I);

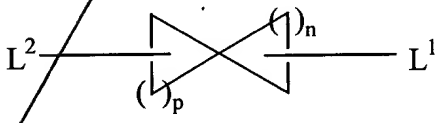


(II)

wherein n and p are independently 0-4 and the sum of n and p is 1 to 6;



(III); and



(IV)

wherein n and p are independently 1-4.

wherein, in each of structures (I) to (IV):

one or more of the ring carbon atoms not bound to L^2 or L^1 may be optionally replaced with NR^1, where R^1 is hydrogen or a noninterfering substituent; or by CHR^2 or CR^2_2, where R^2 is a noninterfering substituent other than hydrogen; and

one or both of the ring carbon atoms bound to L^2 and L^1 may be independently replaced with CR^3 or N where R^3 is independently a noninterfering substituent other than hydrogen.

11. The compound of claim 10 wherein R^2 and R^3 are independently selected from the group consisting of alkyl, alkenyl, alkynyl, aryl, arylalkyl, acyl, aroyl, heteroaryl, heteroalkyl, heteroalkenyl, heteroalkynyl, heteroalkylaryl, NH-aroyl, halo, OR, NR_2, SR, SOR, SO_2R, OCOR, NRCOR, $NRCONR_2$, NRCOOR, $OCONR_2$, RCO, COOR, alkyl-OOR, SO_3R, $CONR_2$, SO_2NR_2, $NRSO_2NR_2$, CN, CF_3, R_3Si, and NO_2, wherein each R is independently H, alkyl, alkenyl or aryl or heteroforms thereof and two of R^2 and/or R^3 on adjacent positions can be joined to form a fused, optionally substituted aromatic or nonaromatic, saturated or unsaturated ring which contains 3-8 members, or R^2 and/or R^3 is =O or an oxime, oximeether, oximeester or ketal thereof.

12. The compound of claim 11 wherein R^2 and R^3 are independently selected from halo, OR and alkyl.

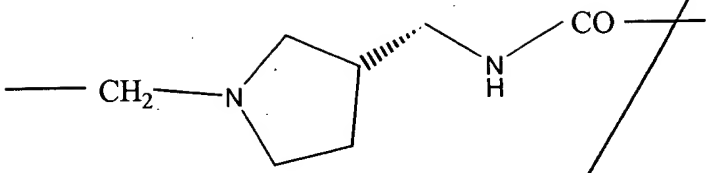
13. The compound of claim 10 wherein moiety L^2-X-L^1 is structure (I).

14. The compound of claim 11 wherein the ring carbon bonded to L^1 is replaced with N; or the ring carbon bonded to L^2 is replaced with N; or both of said ring carbons are replaced with N.

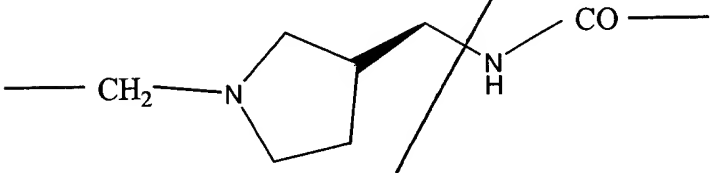
15. The compound of claim 14 wherein the ring carbon bonded to L^2 is replaced with nitrogen and the ring atom bonded to L^1 is carbon.

16. The compound of claim 14 wherein L^2 is methylene; and –L1- is $-CH_2-NH-CO-$ such that the portion of the compound represented by -X-L^1- consists of $-X-CH_2-NH-CO-$.

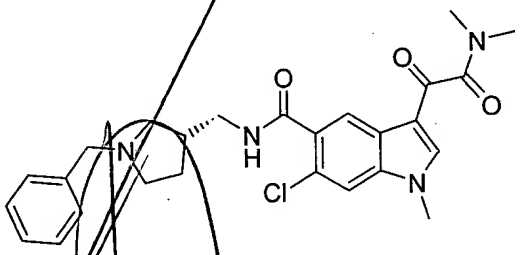
17. The compound of claim 16 wherein L^2-X-L^1 is selected from:



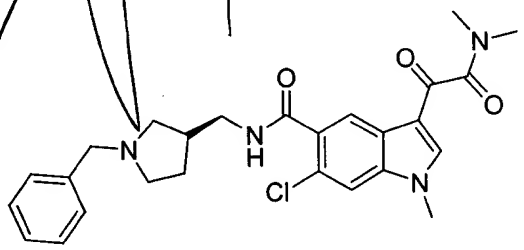
and



18. The compound of claim 17 wherein the compound is:



19. The compound of claim 17 wherein the compound is:



20. The compound of claim 10 wherein L^2-X-L^1 is structure (II).

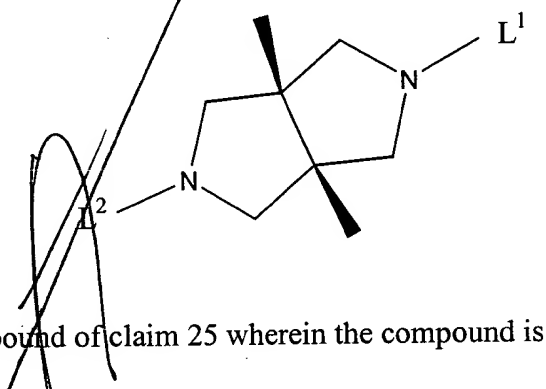
21. The compound of claim 20 wherein n and p in structure (II) are both 1.

22. The compound of claim 21 wherein the ring carbon bonded to L^1 is replaced with N; or the ring carbon bonded to L^2 is replaced with N; or both of said ring carbons are replaced with N.

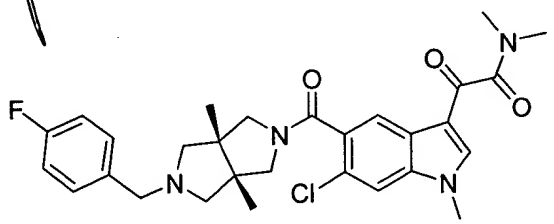
23. The compound of claim 22 wherein both of said ring carbons bonded to L^1 and L^2 are replaced with N.

24. The compound of claim 23 wherein one or more of the ring carbon atoms are methyl substituted.

25. The compound of claim 24 wherein L^2-X-L^1 is:



26. The compound of claim 25 wherein the compound is:



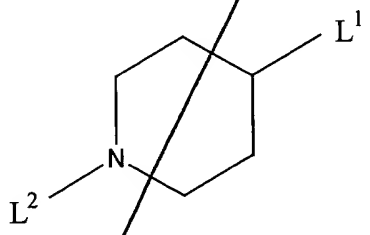
27. The compound of claim 20 wherein n and p are both 2.

28. The compound of claim 20 wherein one of n and p = 1 and the other = 2.

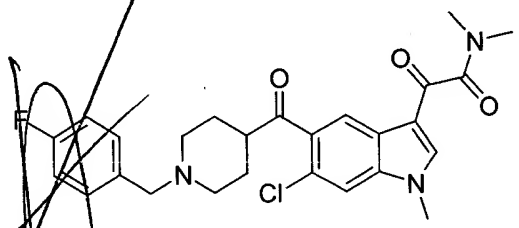
29. The compound of claim 10 wherein L^2-X-L^1 is structure (III).

30. The compound of claim 28 wherein the ring carbon bonded to L^2 is replaced with nitrogen and the ring atom bonded to L^1 is carbon.

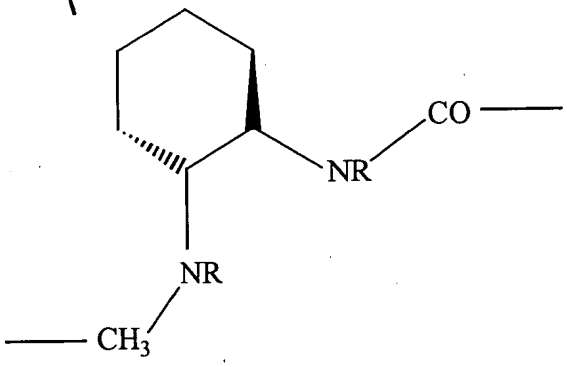
31. The compound of claim 30 wherein L^2-X-L^1 is:



32. The compound of claim 31 wherein the compound is:

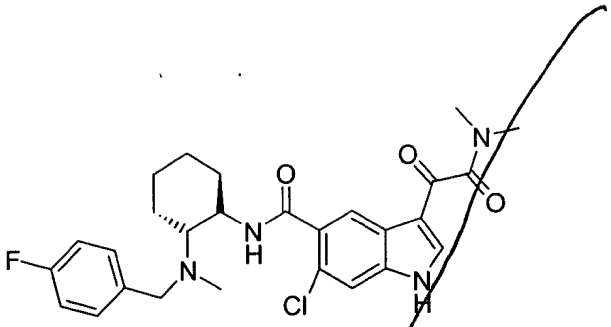


33. The compound of claim 29 wherein L2-X-L^1:



where R is H or a noninterfering substituent.

34. The compound of claim 33 wherein the compound is:

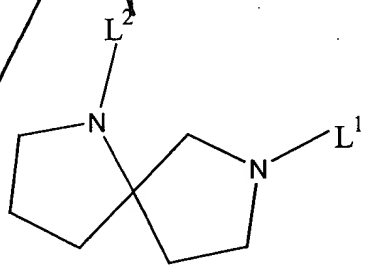


35. The compound of claim 10 wherein L^2-X-L^1 is structure (IV).

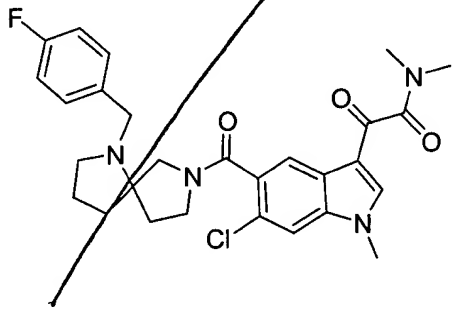
36. The compound of claim 35 wherein the ring carbon atom of X bonded to L^2 is replaced with nitrogen; or the ring carbon atom bonded to L^1 is replaced with nitrogen; or both of said ring carbons are replaced with nitrogen.

37. The compound of claim 36 wherein n and p in L^2-X-L^1 are both 2.

38. The compound of claim 37 wherein L^2-X-L^1 is:



39. The compound of claim 38 wherein the compound is:



40. The compound of claim 1 wherein L^1 and L^2 are independently selected from CO, CHOH, CH_2-NH-CO, CH_2-N-CH3, and CH_2.

41. The compound of claim 40 wherein L^1 and/or L^2 is CO.

42. The compound of claim 41 wherein L^1 and/or L^2 is CH_2-NH-CO.

43. The compound of claim 41 wherein L^1 and/or L^2 is CH_2-N-CH3.

44. The compound of claim 1 wherein L^2 is alkylene (1-4C), alkenylene (1-4C), heteroalkylene (1-4C) or hetero alkyenylene, wherein the foregoing are optionally substituted with a moiety selected from the group consisting of alkyl, alkenyl, alkynyl, aryl, arylalkyl, acyl, aroyl, heteroaryl, heteroalkyl, heteroalkenyl, heteroalkynyl, heteroalkylaryl, NH-aroyl, halo, OR, NR_2, SR, SOR, SO_2R, OCOR, NRCOR, $NRCONR_2$, NRCOOR, $OCONR_2$, RCO, COOR, alkyl-OOR, SO_3R, $CONR_2$, SO_2NR_2, $NRSO_2NR_2$, CN, CF_3, R_3Si, and NO_2, wherein each R is independently H, alkyl, alkenyl or aryl or heteroforms thereof, and wherein two substituents on L^2 can be joined to form a non-aromatic saturated or unsaturated ring that includes 0-3 heteroatoms which are O, S and/or N and which contains 3 to 8 members or said two substituents can be joined to form a carbonyl moiety or an oxime, oximeether, oximeester or ketal of said carbonyl moiety.

45. The compound of claim 44 wherein L^2 and/or L^1 is unsubstituted alkylene.

46. The compound of claim 44 wherein L^2 and/or L^1 is unsubstituted methylene, methylene substituted with alkyl, or -CH=.

47. The compound of claim 1 wherein Ar is optionally substituted with 0-5 substituents selected from the group consisting of alkyl, alkenyl, alkynyl, aryl, arylalkyl, acyl, aroyl, heteroaryl, heteroalkyl, heteroalkenyl, heteroalkynyl, heteroalkylaryl, NH-aroyl, halo, OR, NR_2, SR, SOR, SO_2R, OCOR, NRCOR, $NRCONR_2$, NRCOOR, $OCONR_2$, RCO, COOR, alkyl-OOR, SO_3R, $CONR_2$, SO_2NR_2, $NRSO_2NR_2$, CN, CF_3, R_3Si, and NO_2, wherein each R is independently H, alkyl, alkenyl or aryl or heteroforms thereof, and wherein two of said optional substituents on adjacent positions can be joined

to form a fused, optionally substituted aromatic or nonaromatic, saturated or unsaturated ring which contains 3-8 members.

48. The compound of claim 47 wherein Ar is optionally substituted phenyl.

49. The compound of claim 48 wherein said optional substitution is by halo, OR, or alkyl.

50. The compound of claim 49 wherein said phenyl is unsubstituted or has a single substituent.

51. The compound of claim 1 wherein each R^1 is halo, alkyl, heteroalkyl, OCOR, OR, NRCOR, SR, or NR_2, wherein R is H, alkyl, aryl, or heteroforms thereof.

52. The compound of claim 51 wherein R^1 is halo or alkoxy.

53. The compound of claim 52 wherein n is 0, 1 or 2.

54. The compound of claim 1 wherein L^1 is coupled to the α ring at the 4-, 5- or 6-position.

55. The compound of claim 1 wherein Z^2 at position 3 is CA or CHA.

56. The compound of claim 55 wherein the Z^2 at position 2 is CR^3 or CR^3_2.

57. The compound of claim 56 wherein R^3 is hydrogen, or is alkyl, alkenyl, alkynyl, aryl, arylalkyl, acyl, aroyl, heteroaryl, heteroalkyl, heteroalkenyl, heteroalkynyl, heteroalkylaryl, NH-aroyl, halo, OR, NR_2, SR, SOR, SO_2R, OCOR, NRCOR, $NRCONR_2$, NRCOOR, $OCONR_2$, RCO, COOR, alkyl-OOR, SO_3R, $CONR_2$, SO_2NR_2, $NRSO_2NR_2$, CN, CF_3, R_3Si, and NO_2, wherein each R is independently H, alkyl, alkenyl or aryl or heteroforms thereof and two of R^1 can be joined to form a fused, optionally

substituted aromatic or nonaromatic, saturated or unsaturated ring which contains 3-8 members.

58. The compound of claim 57 wherein each R^3 is selected from the group consisting of H, alkyl, acyl, aryl, arylalkyl, heteroalkyl, heteroaryl, halo, OR, NR_2, SR, NRCOR, alkyl-OOR, RCO, COOR, and CN, wherein each R is independently H, alkyl, or aryl or heteroforms thereof.

59. The compound of claim 55 wherein Z^2 at position 2 is N or NR^4.

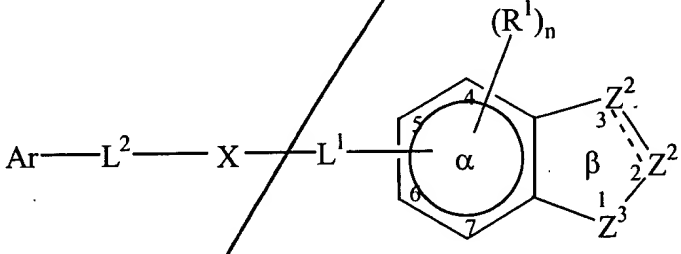
60. The compound of claim 59 wherein R^4 is H, or alkyl, alkenyl, alkynyl, aryl, arylalkyl, acyl, aroyl, heteroaryl, heteroalkyl, heteroalkenyl, heteroalkynyl, heteroalkylaryl, or is SOR, SO_2R, RCO, COOR, alkyl-COR, SO_3R, $CONR_2$, SO_2NR_2, CN, CF_3, or R_3Si wherein each R is independently H, alkyl, alkenyl or aryl or heteroforms thereof.

61. The compound of claim 1 wherein ⩫ represents a double bond.

62. The compound of claim 1 wherein the distance between the atom on Ar bonded to L^2 and the atom of the α ring bonded to L^1 is 7.5-11Å.

63. A pharmaceutical composition for treating conditions characterized by enhanced p38-α activity which composition comprises

a therapeutically effective amount of a compound of the formula



(1)

and the pharmaceutically acceptable salts thereof, or a pharmaceutical composition thereof, wherein

Ar is an aryl group substituted with 0-5 non-interfering substituents, wherein two adjacent noninterfering substituents can form a fused aromatic or nonaromatic ring;

L^1 and L^2 are linkers;

X is an aliphatic monocyclic or aliphatic polycyclic moiety optionally comprising one or more hetero ring atoms wherein the cyclic moiety may be optionally substituted with one or more noninterfering substituents and where said optional substituents may constitute a ring fused to X;

n is 0-3;

each R^1 is hydrogen or a noninterfering substituent;

 represents a single or double bond;

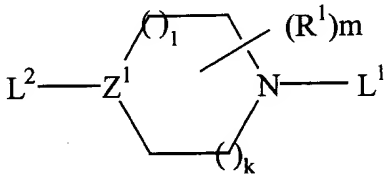
one Z^2 is CA or CR^2A; the other Z^2 is CR^3, CR^3_2, NR^4 or N; and each R^2, R^3 and R^4 is independently hydrogen or a noninterfering substituent;

Z^3 is NR^5 or O; where R^5 is hydrogen or a noninterfering substituent;

A is $-W_i-COX_jY$, where Y is COR^6 or an isostere thereof, each of W and X is a spacer of 2-6Å; each of i and j is independently 0 or 1; and R^6 is a noninterfering substituent;

and wherein the smallest number of covalent bonds in the compound separating the atom of Ar linked to L^2 and the atom of the α ring linked to L^1 is at least 5, each said bond having a bond length of 1.2 to 2.0 angstroms; and/or the distance in space between the atom of Ar linked to L^2 and the atom of the α ring linked to L^1 is 4.5 –24 angstroms;

and with the proviso that the portion of the compound represented by L^2-X-L^1 is not:

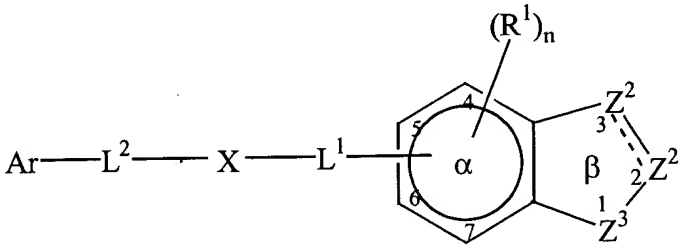


where L^2 and L^1 are linkers; Z^1 is CR or N wherein R is hydrogen or a non-interfering substituent; each R^1 is independently a non-interfering substituent; and each of l and k is 0-3; and m is 0-4.

64. The composition of claim 63 which further contains an additional therapeutic agent.

65. The composition of claim 64 wherein said additional therapeutic agent is a corticosteroid, a monoclonal antibody, or an inhibitor of cell division.

66. A method to treat a condition mediated by p38-α kinase comprising administering to a subject in need of such treatment a compound of the formula:



(1)

and the pharmaceutically acceptable salts thereof, or a pharmaceutical composition thereof, wherein

Ar is an aryl group substituted with 0-5 non-interfering substituents, wherein two adjacent noninterfering substituents can form a fused aromatic or nonaromatic ring;

L^1 and L^2 are linkers;

X is an aliphatic monocyclic or aliphatic polycyclic moiety optionally comprising one or more hetero ring atoms wherein the cyclic moiety may be optionally substituted with one or more noninterfering substituents and where said optional substituents may constitute a ring fused to X;

n is 0-3;

each R^1 is hydrogen or a noninterfering substituent;

 represents a single or double bond;

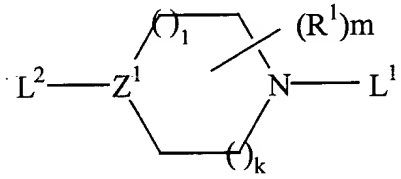
one Z^2 is CA or CR^2A; the other Z^2 is CR^3, CR^3_2, NR^4 or N; and each R^2, R^3 and R^4 is independently hydrogen or a noninterfering substituent;

Z^3 is NR^5 or O; where R^5 is hydrogen or a noninterfering substituent;

A is $-W_i-COX_jY$, where Y is COR^6 or an isostere thereof, each of W and X is a spacer of 2-6Å; each of i and j is independently 0 or 1; and R^6 is a noninterfering substituent;

and wherein the smallest number of covalent bonds in the compound separating the atom of Ar linked to L^2 and the atom of the α ring linked to L^1 is at least 5, each said bond having a bond length of 1.2 to 2.0 angstroms; and/or the distance in space between the atom of Ar linked to L^2 and the atom of the α ring linked to L^1 is 4.5 –24 angstroms;

and with the proviso that the portion of the compound represented by L^2-X-L^1 is not:



where L^2 and L^1 are linkers; Z^1 is CR or N wherein R is hydrogen or a non-interfering substituent; each R^1 is independently a non-interfering substituent; and each of l and k is 0-3; and m is 0-4.

67. The method of claim 66 wherein said condition is a proinflammation response.

68. The method of claim 67 wherein said proinflammation response is multiple sclerosis, IBD, rheumatoid arthritis, rheumatoid spondylitis, osteoarthritis, gouty arthritis, other arthritic conditions, sepsis, septic shock, endotoxic shock, Gram-negative sepsis, toxic shock syndrome, asthma, adult respiratory distress syndrome, stroke, reperfusion injury, CNS injury, psoriasis, restenosis, cerebral malaria, chronic pulmonary inflammatory disease, silicosis, pulmonary sarcosis, a bone resorption disease, graft-versus-host reaction, Crohn's Disease, ulcerative colitis, Alzheimer's or pyresis.